Figs. 9A-C are amended to include element numbers listed in the paragraph bridging pages 11-12 for these figures.

REMARKS

This Preliminary Amendment corrects obvious typographical and clerical errors in the claims and specification. None of the amendments adds new matter to the application. To facilitate entrance of this amendment a replacement specification is provided herewith incorporating the amendments made herein. The replacement specification provided does not include any amendments other than those described herein and does not add new matter to the application.

Amendment of the claims:.

Spelling error, repeated words, punctuation errors, verb/subject agreement and similar clerical errors have been corrected in claims 21, 31, 38, 47, 60, 61, 62, 76, 80, 82, 83, 95, 100, 101, 107, 110, 124, and 126.

Claim 17 has been made dependent upon claim 2 rather than claim 1 to insure more clear antecedent basis because the word "cell" is recited in claim 2 , but not in claim 1.

Claims 25, 62-67 and 127 have been amended to recite "one or more of the signal recognition elements" to correct antecedent basis. The claims have also been amended for consistency with this amendment. These claims depend from claim 1 which recites "a plurality of signal recognition elements." This language is also consistent with recitation of "one or more" employed in claims 60 and 61.

Claim 45 has been amended to correct an obvious clerical omission of the word "to."

Claim 52 has been amended to correct an obvious clerical omission of the word "of."

Claims 70 and 71 have been amended to delete the word 'between" which is believed to be redundant in view of the recitations "about 10 to 25 " and "2 to about 10." The phrase "to about" is believed to convey the idea of "between."

The chemical structure in claim 91 has been replaced to change the variables L^{11} and L^{12} with L^1 and L^2. This amendment is made for consistency with variable definitions in the

specification.

In claim 81 the phrase "an optional linker groups" has been corrected to "optional linker groups" for proper usage . A similar phrase in claim 91 has been amended to be consistent with the language in claim 81. The phrase used in claims 81 and 91 is now also consistent with the similar phrase used in claim 107.

This amendment adds new claims 132-141 which are added to more completely claim that which Applicants consider to be their invention. These new claims are fully supported by the specification and the claims as-filed. Specific support for the method claim 132 is found on page 19, lines 13-15 of the specification as filed. Specific support for FE providing for attachment to surfaces is found on page 17, lines 16-18.

Amendment of the Specification

A number of clerical errors whose correction is obvious have been corrected by the amendment submitted herewith.

The first chemical formula on the top of page 27 (as filed) has been amended to replace variable listed therein as L^{11} and L^{12} with the variables L^1 and L^2. The definitions of variables below the formulas refers only to L^1 and L^2 which are employed in all other structures. The formula was amended for consistency with the specification definitions.

The specification has been amended at page 38 to include element numbers for two features identified in Fig. 6. This amendment accompanies an amendment of Fig. 6 to add these numbers. The relationship between the figure elements and the description of the elements is clear from the context of the specification and Fig. 6. This amendment is made in part to formalize Fig. 6 and to make the specification and the Figures consistent in language.

Scheme 1 of the specification has been amended to replace the structure of compounds designated **9** and **10-13**. The specification as filed on page 43 describes these compounds as having mannose residues. The structure provided in Scheme 1 of these compounds had an incorrect sugar residue and has been replaced with the structure of mannose. The structure of these compounds was properly drawn in the provisional application from which this application takes priority and which is incorporated by reference herein. The structures where labeled as

compounds **61** and **61-64** in Figure 18 of the provisional application. This amendment is supported by the description in the specification and the description and figures of the provisional application and also represents the correction of an error the correction of which would be obvious to one or ordinary skill in the art.

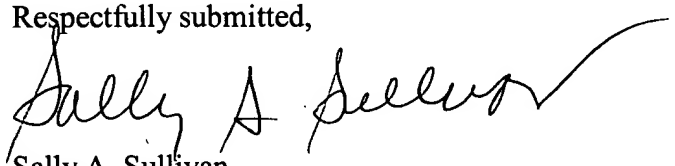
None of the amendments to the specification represents the addition of new matter.

Applicants request approval of certain amendments to the drawings. These amendments add elements numbers to the drawings for consistency between the drawings and the specification (Figs. 7A-D or Figs. 9A-C) and add element numbers to Fig. 6 to identify elements discussed in the specification. These amendments are intended to formalize the drawings and do not add new matter to the specification.

Conclusion

Claims 1-141 are now in the application. A check in the amount of $242 accompanies this submission for the addition of 1 independent claim ($80) and 9 independent claims ($162). It is believed that no additional fees are required. If the enclosed amount is incorrect, please charge any deficiency or credit any overpayment to deposit account 07-1969.

Respectfully submitted,



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MARKED-UP AMENDMENTS TO THE SPECIFICATION

USSN 09/815,296

Page 1, third full paragraph

A variety of biological processes are mediated by the binding of one chemical or biological species, macromolecule or particle (e.g., a cell, virus or virion) to another chemical or biological species, macromolecule or particle. In many cases there is evidence that the valency of the binding may be an important aspect of the mechanism of the mediation of the biological process. The present invention relates to compounds and methods for selectively varying the valency <u>of</u> such interactions employing multivalent ligands to which a plurality of chemical or biological species involved in binding to other chemical or biological species <u>are</u> (generally designated recognition elements, RE, herein) attached in a controlled fashion, with control over the number of RE, the spacing of RE and the relative orientation of RE. Certain recognition elements are involved directly or indirectly in biological signaling processes. [o]<u>O</u>ther recognition elements are involved simply in facilitating binding that is associated with the biological process. This invention then is generally related to the control of biological processes by controlling the structure of such multivalent ligands. The multivalent ligands of this invention have applications particularly in cell signaling processes and more generally in macromolecular assembly of recognition elements that are involved in biological processes.

Paragraph bridging pages 3 and 4

This invention provides multivalent ligands which carry or display at least one recognition element (RE), and preferably a plurality of recognition elements, for binding directly or indirectly to cells or other biological particles or more generally [by] <u>for</u> binding to any biological molecule. The multivalent ligands provided can most generally function for binding or targeting to any biological particle or molecule and particularly [to] <u>for</u> targeting of cells or

cell types or viruses, for cell aggregation and generally for macromolecular assembly of biological macromolecules. The multivalent ligands of this invention are generally applicable for creating scaffolds (assemblies) of chemical or biological species, including without limitation, antigens, epitopes, ligand binding groups, ligands for cell receptors (cell surface receptors, transmembrane receptors and cytoplasmic receptors), and various macromolecules (nucleic acids, carbohydrates, saccharides, proteins, peptides, etc.). In these scaffolds, the number, spacing, relative positioning and relative orientation of recognition elements can be controlled.

Paragraph bridging pages 4 and 5

Scaffolded multivalent ligands of this invention which comprise a plurality of RE, SRE or both optionally [incombination] in combination with FE can be employed in a variety of diagnostic and clinical applications, in particular in blood typing and in pathogen detection. The multivalent ligands herein can be employed in the detection of various biological molecules and particles (cells and viruses) and in a variety of assay methods(histology, Western blots, PCR assays, ELISA assays, agglutination assays, among others). In general, [increased] increases in valency in such ligands will be associated with an increase in assay or diagnostic sensitivity.--

Page 7, third full paragraph

A given cell receptor may mediate more than one biological response. The multivalent ligands of this invention that carry ligands which bind to a given cell receptor, but which do not induce a biological response mediated by that receptor, may be employed to inhibit the biological response.

Page 8, first full paragraph

Multivalent ligands of this invention can be employed in methods to modulate signal transduction processes (i.e., the transmission of information between the outside and the inside of a cell and between cells, in biological systems) in prokaryotic or eukaryotic cells. The methods can be practiced *in vivo*, *in vitro* or *ex vivo* (where cells are removed from a natural environment, including a multicellular organism, and are intended once treated to be returned to

that environment). For example, chemotaxis or cell migration responses to SREs can be modulated. Such methods are applicable to [both prokaryotic] prokaryotes (e.g., Gram negative, as well as Gram positive bacteria), eukaryotic microorganisms (including, without limitation, eukaryotic parasites and pathogens of various organisms, including mammals), and eukaryotic cells of larger organisms including those of mammals, and specifically including those of humans (e.g., leukocytes, lymphocytes, endothelial cells, and epithelial cells). Multivalent ligands that modulate responses in bacterial cells or in eukaryotic cells, including eukaryotic pathogens or parasites, can be used to inhibit proliferation, colonization, migration, or biofilm formation by the bacterium, or eukaryotic pathogen or parasite and, as a consequence, can inhibit infection or colonization by such microorganisms.

Page 8, second full paragraph

Multivalent ligands can also be used to promote or inhibit cell differentiation, cell proliferation and/ or cell death (e.g., apoptosis). Multivalent ligands that modulate responses in eukaryotic cells of larger organisms can be used to inhibit undesired cell proliferation, undesired migration and undesired formation of cell to cell junctions or to promote or enhance desired cell proliferation, [desire] desired migration and desired formation of cell junctions dependent upon the selection of SRE and other FE in the multivalent ligand.

Page 10, first full paragraph

Figure 1 schematically illustrates several ways in which multivalent [ligand] ligands of this invention can functions in macromolecular assembly and as effectors of biological responses.

Page 10, second full paragraph

Figure 2A: Results of video microscopy motion analysis experiments[(I)]. Bacteria *(Escherichia coli*) were treated with buffer alone, galactose, or compound **1** or **3** (Scheme 1) at the indicated saccharide concentrations. The results represent the average from at least five independent experiments performed in triplicate. Error bars represent the deviation between per-second averages during the ten second interval.

Page 10, fourth full paragraph

Figures 3A and 3B: Results of *E. coli* capillary accumulation assays. The number of bacteria accumulated is plotted versus the concentration of the attractant (galactose or compounds **1** -**4**, Scheme 1) calculated on a saccharide residue basis. (A): Results are shown for capillaries filled with buffer alone[(0)], compound **1** [(1)], and compound **2** [(2)] or (B): buffer alone[(0)], compound **3** [(3)] and compound **4** [(4)] at the indicated concentrations. The vertical line at 1 mM indicates the concentration of maximum chemotaxis for the monomeric compound **1**. The concentrations used in this assay are not directly comparable to those used in the motion analysis experiments (see Figure 2A), because the gradient formed in the capillary assay is not defined. Results are the average of 3 to 6 experiments performed in duplicate and error bars represent a single standard deviation. Partial permeabilization was required to obtain chemotaxis towards **4**, and was utilized for all experiments [57].

Page 10, fifth full paragraph

Figure 4: Results of *B. subtilis* capillary accumulation assays using ROMP-derived glucose ligands (compound **5** -**7**, Scheme 1). Buffer alone, glucose, or glucose-bearing compounds **5**-**7** were used as attractants in the capillary accumulation assay. Results are shown for glucose[(G)], compound **5** [(5)], compound **6** [(6)], and compound **7** [(7)]. Results are the average of at least four trials performed in duplicate and error bars represent single standard deviations.

Paragraph bridging pages 10 and 11

Figures 5A and B: Results of video microscopy motion analysis experiments [(II)]. (A): Bacteria (*E. coli)* were treated with increasing concentrations of serine (μM) after initial treatment (followed by a 2 min adaptation period) with buffer alone (■) or 10μM attractant: galactose (●), compound **1** (10mer, ▲) or compound **3** (25 mer,◆); (B) Bar graph of data for angular mean velocity taken from Fig. 6A at serine concentration 1μM. Initial treatment with compound **3** results in a significant enhancement of bacterial response to serine. Angular mean velocities varied approximately 14% between experiments performed on different days.

Page 12, first full paragraph

Figure 10: Bar graph illustrating that ConA clusters assembled on ROMP-derived scaffolds are able to form aggregates of Jurkat cells. Percent of Jurkat cells present in aggregates is plotted against the treatment. ConA at 100 μg/mL or 5 μg/mL is able to form aggregates. Aggregate formation could be inhibited by addition of 50 mM methyl α-D-mannopyranoside (α man). Compounds [**9-12**ere] **9-12** were added to a final mannose concentrations of 0.5 μM or 5 μM along with a final ConA concentration of 5 μg/mL. Results are the average of at least three independent experiments and error bars represent single standard deviations.

Page 12, fourth full paragraph

The multivalent ligands of this invention are molecular scaffolds to which a plurality of functional or structural groups, particularly RE and/or SREs, are bonded, to present a display of the [functionalor] functional or structural groups in a productive manner. The scaffold can in general be formed from any chemical or biological species that provides the desired orientation of display. In addition to linear arrays, the scaffolds can be chosen to provide arrays of functional groups with selected non-linear presentation. See, for example, the various non-linear scaffold structures illustrated in Fig. 8.

Page 13, second full paragraph

The RE, SRE and any FE can be bonded on to the molecular scaffold randomly or to a pre-selected [patern] pattern in which the [arragement] arrangement of the RE, SRE and FE along the length of the scaffold matches a selected pattern, e.g., alternating different SRE or RE, [slelcted] selected spacing of different SRE or RE and the like[)].

Page 13, third full paragraph

The molecular scaffold can be rigid or flexible, hydrophilic or hydrophobic, symmetrical or unsymmetrical, have large surface area or small surface area, and interact or not with cell surface receptors. The molecular scaffold can be any of a variety of oligomers or polymers,

including without limitation, polyacrylamides, polyesters, polyethers, polymethacrylates, polyols, and polyamino acids and corresponding oligomers. Molecular scaffolds can in general be linear polymers, branched polymers or cross-linked polymers. Preferred molecular scaffolds are biocompatible. Molecular scaffolds prepared by ROMP methods, as illustrated in several formulas herein, are preferred. Molecular scaffolds can be hydrophobic or can be made to be more hydrophilic by substitution with polar substituents, such as -OH. The scaffold can be substituted, in general, with any groups that do not interfere with signal activity and which provide desirable chemical and physical properties.

Page 15, first full paragraph

A chemoattractant is a chemical or biological signal toward which a cell migrates. The cell senses increasing concentrations of the chemoattractant and moves toward higher concentrations. Cell sensing mechanisms for chemoattractants are often very sensitive. Alternatively, cells may, in response to other signals, move to lower concentrations of signal. Bacterial cells migrate toward certain nutrients, such as glucose or galactose or amino acids, such as serine. Leukocytes (white blood cells) migrate toward, [N-formly] N-formyl peptides and other derivatized peptides, the activated component of CS (CSa), platelet-activating factor(PAF), leukotriene B4 (LTB4), or chemotactic cytokines (i.e., chemokines, including α- and β-chemokines) (65). N-formylated peptides are products of bacterial protein synthesis and signal bacterial infection. The receptors for N-formylated peptides may also bind to other derivatized peptides such as N-acyl-peptides. Thus any ligand (which may include species that act as agonist or antagonists of receptor function) of a N-formylated peptide receptor may be employed for applications related to that receptor. Neutrophils, one type of leukocyte, are guided to the site of bacterial infection by sensing low levels of N-formylated peptides. Once at the site of infection phagocytosis can occur. A chemoattractant may induce biological responses in addition to migration or chemotaxis. For example, in various types of leukocytes, chemoattractants can induce the release of toxic species or the release of [inflamatory] inflammatory cytokines, transcription factors and other chemical species which, in turn, function as chemical signals for other cells.

Page 16, first full paragraph

The term epitope is used generally herein to refer to any chemical species that functions as an antigenic determinant and most [term] generally includes all antigens. Epitopes are those parts of an antigen that combine with an antigen-binding site on an antibody molecule or on a lymphocyte (e.g., B cells and T cells) receptor. Binding of the epitope can, for example, stimulate antibody production or T cell responses. Epitopes may exhibit different levels of immunogenicity. Those that are more immunogenic than others and which dominant the overall antigenic response are designated immunodominant epitopes. Most non-self proteins and many carbohydrates are antigens, so epitopes include, without limitation, proteins fragments (e.g., peptides) and carbohydrate fragments (e.g., saccharides and oligosaccharides). As used herein the term "self" as applied to antigen, epitope or cell is an entity that is recognized by an immune cell, a combination of immune cells or an immune system as self. The term "self" may also be applied other biological particles that are recognized as self by an immune cell, or cells or an immune system. Some [anitgens,] antigens, epitopes, cells and particles that are recognized as self are [acutally] actually foreign to the immune cell, cells or immune system, but are not so recognized. As used herein the term "foreign" as applied to antigen, epitope or cell is an entity that is recognized by an immune cell, a combination of immune cells or an immune system as foreign. Foreign is also any thing that is not recognized as self, i.e., non-self antigens, etc. The term "foreign" may also be applied to other biological particles that are recognized as foreign by an immune cell, or cells or an immune system. Some antigens, epitopes, cells and particles that are recognized as foreign are actually self to the immune cell, cells or immune system, but are not so recognized.

Page 16, second full paragraph

The term hapten takes its generally accepted meaning in the [are] art as a small molecule, having at least one of the determinant groups of an antigen, that can combine with an antibody but is not immunogenic unless it acts in conjunction with a carrier molecule. Haptens include, among others, hemocyanins and [nitro-sbustituted] nitro-substituted aromatic compounds, such as dinitrophenyl groups, trinitrobenzene sulphonyl groups, and [dinitrofluorophneyl]

dinitrofluorophenyl groups.

Page 16, third full paragraph

The term [anitbody] antibody as used herein is intended to encompass any protein or protein [fragment that functions] fragments that function as an antibody and is specifically intended to include antibody [fragmetns in cluding] fragments including, among others, Fab fragments.

Page 16, fourth full paragraph

[Lectin] A lectin is any of a large group of hemagglutinating proteins found principally in plant seeds. Certain lectins cause agglutination of erythrocytes of certain blood groups; others stimulate the proliferation of lymphocytes.

Page 17, first full paragraph

The term "biological system" is used generally herein to refer to any *in vivo* or *in vitro* system containing signal transduction elements, e.g., signal receptors and biochemical/biological elements for generating a response. A biological system typically contains at least one cell within any environment with which it interacts. A biological system in the context of the uses of multivalent ligands of this invention must contain at least one receptor which can interact with the ligand. In most applications of multivalent ligands, the biological system must contain at least one cell which can respond to the ligand. The response of a cell to the ligand occurs within the biological [systems] system and as noted above may be an intracellular response, an intercellular response or both. The biological system can, for example, be a cell in a tissue, a cell in an organ or organism, a cell in a mixture of cells, a cell in a tissue culture, a cell in a tissue or biological fluid sample, and can include biological systems *in vivo* and *in vitro*.

Page 17, second full paragraph

"Functional elements (FE)" are chemical or biochemical species (molecules, groups, moieties, etc.) that exhibit some biological or chemical function different from an RE or SRE.

FE can, for example, provide reactive groups or latent reactive groups for attaching another chemical or biological group to a multivalent ligand. For example, an FE can be used to attach a multivalent ligand to a solid surface which may be useful for ligand purification or in applications to analytical or diagnostic assays. FE can be various detectable labels or reporter groups including fluorescent labels, radiolabels and high density labels such as gold [particel] particles bound to ligands (e.g., streptavidin labeled with gold [particles) .] particles). Multivalent ligands incorporating detectable labels or reporter groups can be used, for example, in various analytical or [diagnostics] diagnostic assays. Of particular interest are multivalent ligands of this [ivention] invention that are useful in visualization assays, e.g., for the detection of [bioloigcal] biological particles or molecules in microscopy applications. FE can also exhibit various biological functions, e.g., enzymatic function, ligand-binding function, etc., which may facilitate or enhance a selected application of a multivalent ligand.

Page 18, first full paragraph

Multivalent ligands of this invention can be used to modulate signal transduction in prokaryotic and eukaryotic organisms. The [methods] ligands function in a variety of signal transduction processes. [Prokaryote] Prokaryotes have a highly conserved intracellular signal transduction system, the two component system. The major components of this system are varying numbers of alternating histidine-aspartic acid kinase-mediated phosphorylation events, such as virulence, antibiotic resistance, response to environmental stress and sensing. The components of the two component system are highly conserved in prokaryotes. In contrast, eukaryotes appear to have very few two component systems for signal transduction. This orthogonality makes the two component signaling pathway a prime target for exploitation in therapeutic design for the control of bacterial infection. Major signal transduction systems in eukaryotes are mediated by G-protein-linked receptors and enzyme-linked receptors (including receptor guanylyl cyclases, receptor tyrosine kinases, tyrosine-kinase-associated receptors, receptor tyrosine phosophatases, and receptor serine/threonine kinases). The ability to modulate or regulate signal transduction in these pathways allows control over a wide variety of biological processes in eukaryotic cells and eukaryotic organism (including mammals and specifically

humans) and provides significant opportunity for the design of therapeutics.

Page 18, second full paragraph

Figure 1 illustrates several mechanisms by which multivalent ligands of this invention can [functions] function as effectors of biological response. A multivalent ligand can be involved directly in signaling where SREs on the multivalent ligand bind to cell surface receptors, similar to monomeric ligands, and directly induce (or inhibit) a response. Use of a multivalent ligand of this invention with SRE attached to a molecular scaffold can facilitate receptor clustering or relocalization on the cell surface, localization of second messengers or simply generally increase the affinity by local increase in SRE (ligand) concentration. Multivalent ligands functioning through direct signaling can be employed in a variety of applications, including those based on disruption of biofilm formation or disruption of cell migration, are of particular interest for vaccines, and other therapeutics (cancer treatment and [anitbiotics)] antibiotics).

Paragraph bridging pages 18 and 19

Multivalent ligands of this invention can also be involved indirectly in signaling (see Fig. 1) affecting the response of a cell to another signal or ligand. Multivalent [ligand] ligands may function to sensitize or prime cells for enhanced response to another ligand. Indirect signaling effects may be mediated by clustering or reorganization of one type of cell surface receptor which [effective] effectively results in the localization or reorganization of other types of cell surface receptors. Multivalent ligands functioning through indirect signaling can also be useful in a variety of applications, particularly those based on enhancement of a biological response, and are of particular interest for vaccines adjuvants and modulators of immune responses.

Paragraph bridging pages 19 and 20

Multivalent ligands of this invention also have application simply in binding to or targeting of cells. A multivalent ligand containing at least one recognition element for binding to a cell surface receptor (RE) and containing a functional element (FE) targets the cell with that FE. If FE is a label or reporter group, the multivalent ligand acts to label the cell. If FE has a

biological function, the multivalent ligand targets the cell with that function.

Multivalent ligands that contain a plurality of RE (SRE or both) can function in macromolecular assembly which need not involve any biological signaling function. In such applications, the multivalent ligand need not contain any SRE, the multivalent ligand need only contain more than one recognition element for binding to a cell surface receptor (a recognition element, RE) and preferably a plurality of REs. In such applications, the multivalent ligands directly or indirectly bind to more than one cell resulting in cell aggregation. Cell aggregation may itself trigger a biological response (e.g., the release of signal molecules by a cell), but need not. Multivalent ligands can indirectly cause cell aggregation by binding to a plurality of biochemical species, such as lectins (e.g., Concanavalin A) which in turn bind to cells resulting in cell aggregation. The effect of a multivalent ligand on indirect cell aggregation will be dependent upon the valency of the ligand and on the relative concentrations of the multivalent ligand to the species that causes cell aggregation. At higher concentrations of multivalent ligands with higher valency, binding sites on the species that causes cell aggregation [ma] may be saturated inhibiting cell aggregation. At lower concentrations of multivalent ligand, free binding sites will remain and cell aggregation can occur and can be enhanced by the multivalent ligand. Thus, multivalent ligands of this invention can be selectively designed to inhibit or to facilitate cell aggregation. Multivalent ligands functioning for macromolecular assembly can be useful in a variety of applications, particularly those based on cell aggregation, including, but not limited to diagnostic assays, cancer therapy, and pathogen clearance.

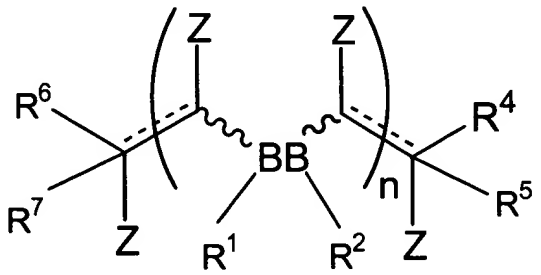
Page 20, second full paragraph

In specific embodiments, linear multivalent ligands of this invention are prepared by ring opening metathesis polymerization [(ROMP,see] (ROMP), see for example (54). This method has been used to prepare multivalent inhibitors of cell functions (27, 28). The ROMP methods have been described in more detail in U.S. patent 5,587,442 relating to multivalent ligands that are polyglycomers. Improvement of ROMP methods for generating block polymers (and oligomers) and for introducing end-groups on ROMP polymers (and oligomers) have been described in U.S. patent applications 09/335,420 and 09/336,121, both filed June 17, 1999. (These U.S. patent

documents are incorporated by reference herein in their entirety particularly for the description of ROMP methods). Scheme 6 illustrates exemplary methods for modification of ROMP backbones, which can be applied in combination with synthetic methods described in the above listed patents and patent applications to synthesize multivalent ligands of this invention. Scheme 6 illustrates a diimide reduction (23, 98, 99) which can be employed to reduce double bonds in ROMP scaffold backbones. Scheme 6 also illustrates the substitution of ROMP scaffold backbones with OH groups using OsO_4 catalyzed [dihydroylation] dihydroxylation (100, 101). Those of ordinary skill [inteh art] in the art can prepare multivalent ligands of this invention, particularly those specifically exemplified in formulas herein, employing the descriptions herein and methods that are well known in the art.

Page 21, first full paragraph

Multivalent ligands of this invention prepared by ROMP are exemplified by the general structure:



wherein:

n is an integer that is 2 or more and represents the number of repeating [unit] units in parentheses that are in the ligand;

the dashed lines indicate [optionalk] optional double bonds;

"BB" represents the backbone repeating unit, which may be cyclic or acyclic, and may be the same or different in a random or block arrangement where [the] the wavy lines indicate

that the BB repeating unit can be in a cis or trans configuration in the backbone;
R^1 and R^2, can be H, an organic group, an FE group or the groups:-L-RE- or -L-SRE- wherein FE is a functional element other than an RE or an SRE, L represents an optional linker group, RE is a recognition element and SRE is a signal recognition element;
R^4 and R^5 are H, or an organic group;
R^6 and R^7 are H, an organic group or an end-group;
Z , independently of other Z in the polymer, is H, OH, OR^8, SH, a halide (F, Br, Cl, I), NH_2 or $N(R^8)_2$ where R^8 is H or an organic group or Z is absent when there is a double bond at the carbon to which A is attached.

Page 22, second full paragraph

RE is a recognition element as discussed above that can be any of a variety of chemical or biochemical species that are recognized by and which [selective] selectively bind to cell receptors, particularly, [transmembrane[transmembrane receptors and cell surface receptors. SRE is a signal recognition element as discussed above that can be any of a variety of chemical or biochemical species that are recognized by one or more cells and which induce a biological response by the cell; "L" is an optional linker group that can provide functional groups for covalent bonding of the RE, SRE or FE to the polymer (oligomer) backbone. FE is a chemical or biochemical functional group other than an SRE, as discussed above. Other examples of ROM scaffolds are illustrated in Schemes 2 and 3.

Page 23, first full paragraph

RE and SRE are attached to the polymer (oligomer) backbone such that they substantially retain their function for binding cell receptors or as signals, respectively. For a given RE or SRE there may be several ways in which it can be bonded into the multivalent ligand, each of which may result in RE that are different in binding affinity or SRE that are different either in binding affinity or in the level or type of response induced. For example, a peptide signal may be bonding through its N-terminus, through its C-terminus or via an amino acid side group, such as through a lysine side group. The site of attachment of an RE or SRE to the multivalent ligand is preferably

selected to minimize loss of binding function (RE) or to minimize loss of signal function (SRE) or alternatively the site of attachment may be selected to maximize signal function (SRE). An RE or SRE may nevertheless exhibit properties that are different from free ligands or free signals (e.g., the binding affinity of an SRE for a cell receptor may be different from that of free signal from which is was derived or which it mimics), but which do not destroy the function of an RE as a ligand or an SRE as a signal. RE can include a variety of known cell receptor ligands and in particular can include lectins. SRE can specifically include monosaccharides (e.g., glucose, galactose), disaccharides, polysaccharides (greater than 2 sugar residues), derivatized saccharides (e.g.,acylated, sialated), peptides, derivatized peptides (e.g., N-formyl peptides), peptoids, various chemoattractants, and various epitopes. Note that a particular chemical or biological species may function as an RE with one type or kind of cell and as an SRE with another type or kind of cell.

Paragraph bridging pages 23 and 24

The linker can provide for spacing of the RE, SRE or FE group(s) from the backbone or can provide for structural flexibility. Linkers may be the same or different on different monomers in the polymer. Linkers that are used in a monomeric scaffold to bond to RE, SRE or FE can also be all the same or different. In a given multivalent ligand carrying one type of [of] RE or SRE group, the linker is preferably the same throughout the [polyme] polymer. Linkers are generally selected so that they are compatible with the intended application of the multivalent ligand and to avoid interference with the function of signal groups. The linker is preferably linear and preferably ranges in length from 1 to about 20 atoms. The linker may contain alicyclic groups (such as a cyclohexyl group). The linker can be an alkyl chain carrying functional groups for bonding to the backbone of the ligand and to the signal. The linker can also be an ether, ester, ketone, amine, amide or thioether chain. In a specific embodiment, the linker can be described as an linear alkyl chain having from 1 to about 20 carbon atoms in length in which one or more non-neighboring CH_2 groups are optionally replaced with an -O-, -S-, -NH-, -NR^{10}-, -CO-, -NH-CO- , -O-CO-, -C=C- , or -C≡C- group, where R^{10} is an alkyl or aryl group. Linker CH_2 groups can be substituted with halogens, alkoxy, or alkyl groups. In the absence of a linker group, the ROMP backbone or the signal group itself must provide the functionality for covalent bonding of the signal to the

backbone. Exemplary linkers include those illustrated in Scheme 3.

Page 24, first full paragraph

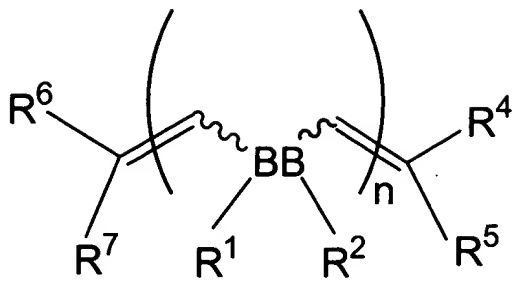
R^1, R^2, R^4, R^5, R^6, R^7, R^8 and R^9 can be organic groups. Organic groups include without limitation alkyl groups, alkenyl groups, and aryl groups as well as substituted alkyl, alkenyl and aryl groups. Substituents for alkyl, alkenyl and aryl groups include halogens (F, Cl, Br, I), -CN, -NO_2, -OH, [ ]-SH, -NH_2, -$N(R^{10})_2$, -SR^{10} and -OR^{10} where R^{10} is an alkyl or aryl group. Aryl groups may also contain alkyl or alkenyl [subtituents] substituents. Organic groups will typically have from 1 to about 20 carbon atoms, and preferably have 1 to about 10 carbon atoms. Alkyl groups may be straight-chain, branched or cyclic (or contain portions that are cyclic). One or more non-neighboring -CH_2- groups in an alkyl or alkenyl group can be replaced with -O-, -S- , -NH- or -NR^{10}, where R^{10} is an alkyl or aryl group.

Page 25, second full paragraph

When prepared by the ROMP methods, such as those described in U.S. patent applications 09/335,420 and 09/336,121, both filed June 17, 1999 (which are incorporated by reference herein in their entirety for methods of synthesis of multivalent ligands), R^4 and R^5 are derived from the metal carbene catalyts, i.e., they are substituents on the metal carbene carbon of the metal carbene catalyst and in specific embodiments are H and a phenyl group. When using ROMP, R^6 and R^7 are typically derived from the capping agent, i.e, are the substituents on the [electron rich] electron-rich alkene capping agent, such as hydrogen in the case of ethyl vinyl ether.

Page 25, third full paragraph

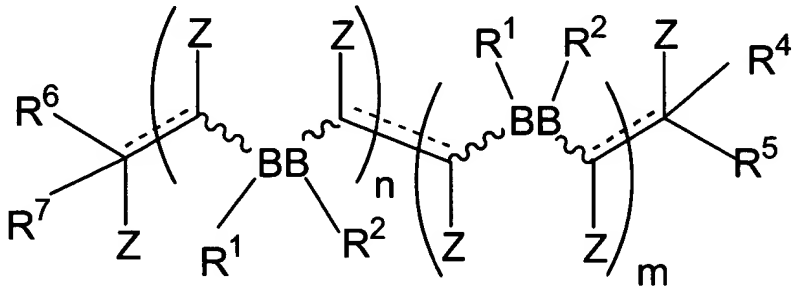
In [aspecificembodiment] a specific embodiment multivalent ligands of this invention include those of formula:



wherein BB, R^{1-2}, and R^{4-7} are as defined above. In specific embodiments, one of R^1 or R^2 is H and the other is L-RE. In specific embodiments, one or R^1 or R^2 is H and the other is L-SRE. In specific embodiments, RE is a lectin or a cell receptor ligand that is comprised within a lectin. In specific embodiments, SRE is a monosaccharide, a disaccharide or a relatively short saccharide having up to about 10 sugar residues. In other specific embodiments, SRE is a peptide or a derivatized peptide (e.g., an N-formyl peptide).

Page 26, first full paragraph

In another specific embodiment the invention relates to multivalent ligands of the formula:

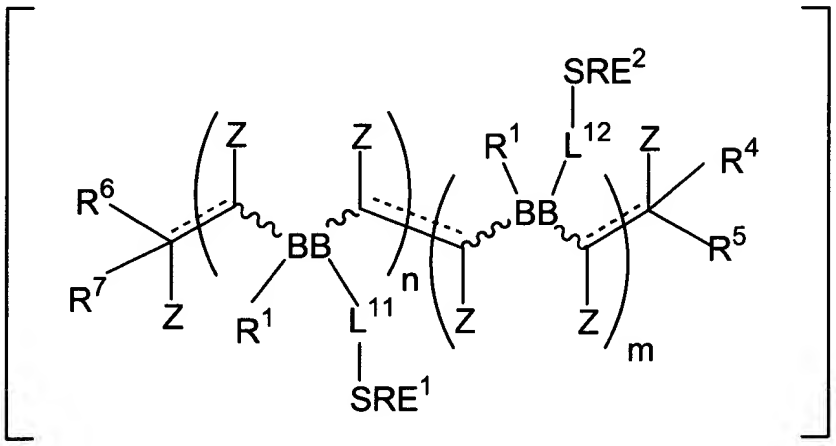


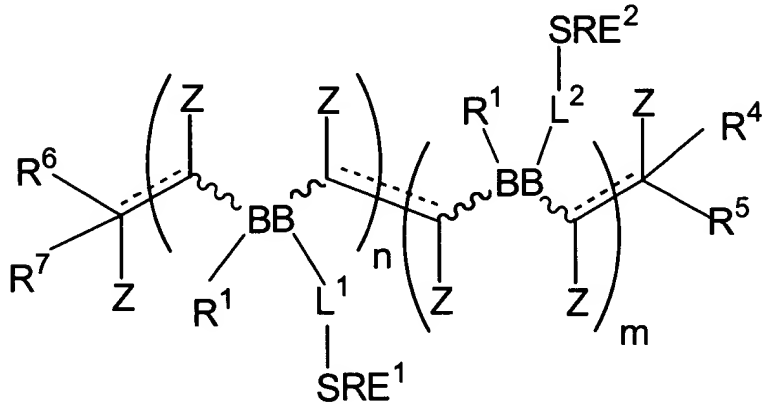
wherein the dashed line indicates an optional double bond and wherein Y, independently of Y in other monomers, R^{1-2}, independent of R^{1-2} in other monomers, and R^{4-7} are as defined above. In specific embodiments, Y is $-CH_2-$. In specific embodiments, one of R^1 or R^2 is H and the other of R^1 or R^2 is -L-RE. In specific embodiments, one of R^1 or R^2 is H and the other of R^1 or R^2 is -L-SRE. R^1 and R^2 together may form an - L-RE or -L-SRE. In yet other specific embodiments, SRE is a peptide or derivatized peptide. When no double bond is present the ring carbons typically carry addition hydrogens, but may be substituted with other groups, such as alkyl groups

having 1-6 carbon atoms or halides that do not [interfer] <u>interfere</u> with the function of any R^1 or R^2 group.

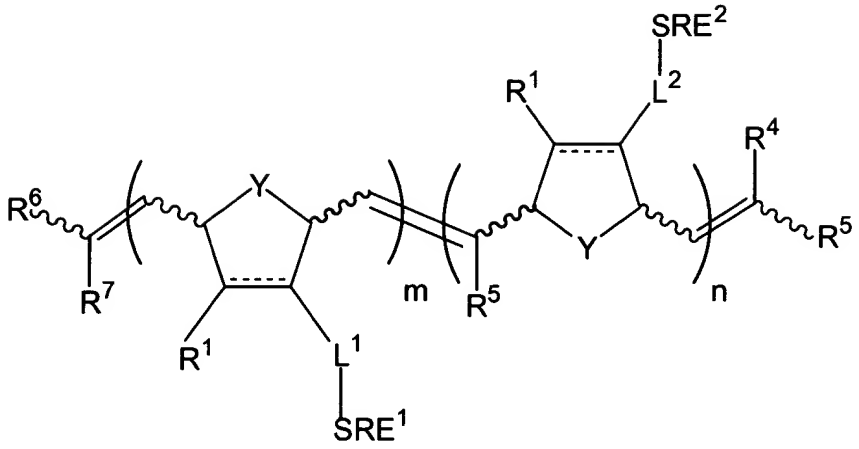
The paragraph bridging pages 26 and 27:

In yet another specific embodiment the invention relates to multivalent ligands of the formulas:





or



in which m is the number of monomers carrying a first SRE (SRE^1) and n is the number of monomers carrying a second SRE (SRE^2). L^1 and L^2 are linkers as described above which may be the same or different. All other variables are as defined in earlier formulas and dashed lines indicating optional double bonds. Both m and n are integers that can range most generally from 1 up to about 10,000, but which more typically will range from 1 to several hundred or several thousand. The value of m may be the same as or different from that of n. In preferred ligands, n + m ranges from 5 or more up to about 200. Multivalent ligands of this invention include those in which n + m ranges between about 10 and 25, those in which n + m is 25 or more, those in which n + m is 50 or more, and those in which n + m is 100 or more. –

Paragraph bridging pages 34 and 35

At pages 34 and 35, please replace the paragraph bridging the pages with the following:

-- Ligands functionalized with galactose such as monovalent ligand 1 and multivalent ligand **3**, also [also serve] serve as attractants in vivo. This was demonstrated by monitoring the behavioral response of E. coli to these ligands. The locomotion behavior of E. coli occurs in two modes, running and tumbling, which are defined by the direction of the flagellar spin and, ultimately, the signal transduction response that arises from interaction of chemoreceptor with ligand [42]. Bacteria in the presence of an attractant will undergo prolonged running responses with low tumbling frequency [42, 43]. To observe the effects of synthetic ligands on tumbling frequency, E. coli were treated with galactose or galactose-bearing ligands, and bacterial motion

was recorded and analyzed using the method of Sager et al. [44]. The tumbling frequency was assessed by averaging the mean angular velocity of the paths obtained in the first 5-15 seconds after addition of attractant (Figure 2A). When bacteria were treated with increasing concentrations of galactose, the mean angular velocity decreased, indicative of a running response. Figures 2B-E illustrate sample paths for representative bacteria treated with buffer alone, galactose, compound **1** and compound **3**. Treatment with monovalent compound **1** produced similar effects to that of the free chemoattractant (galactose), indicating that the anomeric substituent in 1 did not preclude chemotactic activity. Multivalent compound **3** was more active than monovalent 1 or unmodified galactose. Multivalent compound **3** induced a low mean angular velocity even at very low (e.g., 0.001 mM) saccharide residue concentrations. The response of the bacteria to **3** at 0.1 mM saccharide residue concentrations (ca. 0.004 mM concentration) was comparable to that obtained at ten fold higher (1 mM) concentrations of unmodified galactose. The observed differences in concentration of maximum activity between the monomer **1** and multivalent compound **3** demonstrate that ligand valency affects chemotactic activity.

Paragraph bridging pages 35 and 36

When compounds **1-4** were used as attractants in the capillary accumulation assay, oligomer **2** was no more active than monovalent **1**; both elicited a maximum chemotactic response at 1 mM (Figure 3A). Compound **2** displays a higher local concentration of galactose to the receptor, however, the similarity of activities for **1** and **2** indicates that a high local concentration of attractant does not alone give rise to increased chemotactic activity. For compounds **3** and **4**, concentrations of maximum chemotaxis were significantly lower; the maximum for **3** is at a galactose residue concentration of 0.25 mM (ca. 0.01 mM ligand concentration, 100-fold lower than free galactose) and the maximum for **4** is at a galactose residue concentration of 0.10 mM (0.0002 mM ligand concentration). Concentrations of maximum chemotaxis of **3** and **4** are 100- and 5000-fold lower, respectively, than free galactose (Figure 3B). The ligands of higher valency (**3** and **4**), therefore, can induce chemotaxis at extremely low concentrations.

Paragraph bridging pages 37 and 38

To confirm the ability of multivalent ligands to alter the organization of the chemoreceptors in the bacterial membrane *E. coli* were treated with compound **8**, a galactose-bearing multivalent ligand having a fluorescent label (Scheme 1). When *E. coli* were treated with **8** or a fluorescein-labeled anti-Tsr antibody **14**, the fluorescence patterns observed were similar. Both materials were observed to bind at the poles of the bacteria indicating that the ROMP-derived ligands bind specifically to the bacterial chemoreceptors. To address directly the ability of these multivalent ligands to reorganize receptors **15**, *CheW* mutants were treated with both compounds. Patches of anti-Tsr antibody labeled chemoreceptors that colocalize with compound **8** were observed, as illustrated in Fig. 6. This result indicates that multivalent ligand **8** is responsible for the observed changes in cell receptor organization.

Paragraph bridging pages 38 and 39

By generating synthetic molecules using ROMP that differ only in ligand valency, as opposed to ligand density or spacing, it has been shown that the valency of a ligand influences its ability to organize chemoreceptors and its ability to elicit a chemotactic response from those receptors. The results demonstrate that multivalent ligands of distinct valency (distinct or defined number of functional moieties), such as those described herein, can be used to tune cellular responses through changes in receptor organization. Further, ligand valency can be used to tune chemotactic responses of diverse bacteria (both *E. coli* and *Bacillus subtilis*) indicating that the methods of this invention are generally applicable to diverse cell types. The ROMP-based synthetic route to multivalent arrays is general [54] and can be employed to generate a variety of multivalent ligands or arrays which carry a variety of types and numbers of chemical signals that bind to cell receptors (cell surface [recpetors, transmemebrane] receptors, transmembrane receptors and [cytopalsmic] cytoplasmic receptors) and which as a result, likely mediated by lateral receptor reorganization, elicit a biological response. Control of the type of signal covalently bonded to the multivalent ligand and control of the spacing and number of signals presented on the ligand can be used to tune the type and magnitude of the response elicited.

Paragraph bridging pages 40 and 41

The C3d complement fragment binds the CR2 receptor (CD21/CD19 complex) on B cells. The expression fusion product of the fusion of the cloned C3d gene fragment and the C-terminal region of hen egg lysozyme gene was able to increase immunogenicity significantly more (1000-fold) than the level achieved with the lysozyme combined with a strong adjuvant [62]. Scheme 4 illustrates an exemplary multivalent ligand containing two different signal groups **30** prepared from the ROMP polymer **29** by selective covalent bonding of the different signals. One of the signals is a hen egg lysozyme (HEL) peptide (specific for the A20 cell line): 103-117 NGMNAWVAWRNRCKG [(SEQID] (SEQ ID NO: 1)[63] and the other is a 16-mer C3d peptide involved in binding to CR2: KNRWEDPGKQLYNVEA [(SEQID] (SEQ ID NO[;]: 2)[62]. This HEL peptide can be attached to the polymer backbone at the N-terminal amine (**40**) of the peptide or at a side group of a lysine near the end of the peptide (**41**):

40: *GDGNGMNAWVAWRNR-$CONH_2$ [(SEQID] (SEQ ID NO: 3) or

41: DGNGMNAWVAWRNRGK*-$CONH_2$ [(SEQID] (SEQ ID NO: 4)

where * indicates the site of attachment. The C3d peptide can be attached to the multivalent ligand via the thiol of cysteine positioned at either end of the peptide(**42** and **43**):

42: *CKNRWEDPGKQLYNVEA (SEQ ID NO: 5) or

43: KNRWEDPGKQLYNVEAC* (SEQ ID NO: 6)

Page 41, first full paragraph

Multivalent ligands containing signals **41** alone or in combination with **42** or **43** or **40** alone or in combination with **42** or **43** can induce an enhanced immune response compared to HEL its self. A multivalent ligand containing a plurality of peptide elements that are ligands for the CR2 receptor can cluster the CR2 receptor on the surface of the B cell and as demonstrated in the chemotaxis experiments can enhance the response of that B cell to other ligands, e.g., antigens. Multivalent ligands containing one or more bound CR2 ligands in combination with one or more bound antigens can cluster the CR2 receptor with the receptor that recognizes the antigen and thereby enhance the response of the B cell to the antigen. Clustering of CR2 with a

receptor that recognized HEL(for example) on the B cell surface can enhance the response of the B cell for the HEL antigen and can result in an enhancement of immune response toward the HEL epitope. An alternative hen egg lysozyme peptide that can be employed in construction of multivalent ligands of this type is:

44 : ELAAAMKRHGLDNYRGYSLGNWVCA [(SEQID] (SEQ ID NO: 7).

Page 44, second full paragraph

Further experiments were conducted which demonstrated that ConA-mediated agglutination of erythrocytes could be controlled by addition of multivalent ligands (compounds **9-13**). Certain combinations of ConA and multivalent ligands exhibited enhanced agglutination of these cells compared to ConA itself, as shown in Fig. 11. In particular, a combination of ConA tetramer and multivalent ligand (compound **13**) at concentration ration 10:1 (based on tetrameric ConA and based on the number of mannose residues) exhibited significantly [anhanced] enhanced agglutination compared to ConA alone.

Page 45, first full paragraph

Complexes containing multiple Con A tetramers were assembled readily on compounds **10-13** when intermediate multivalent ligand concentrations were used, but were not detectable when the concentration of the scaffold was either too low or too high. The concentration range over which such complexes are formed depends upon the relative concentrations of ConA and multivalent ligand ([bassed] based on the number of ligands, RE or SRE) and upon the valency of multivalent ligand. This is generally true for any complex of a multivalent ligand with any protein. The concentration range over which complexes of a multivalent ligand with one or more ConA (or such complexes with any lectin or more generally with any protein) can be readily determined for a particular application under particular conditions by assessing retention of function by ConA (or more generally the protein or lectin). Complexes of multivalent ligands with ConA will generally be formed, dependent upon the valency of the multivalent ligand and the particular experimental conditions, when the concentration range of the ligand (based on numbers of SRE, e.g., mannose) ranges from about 1:1 to over 100:1.

Page 49, first full paragraph

TEM methods were preformed essentially as previously described [96]. Con A tetramers were labeled with biotin using conditions that favored attachment of 1-2 copies of biotin residues. Biotinylated ConA tetramers were mixed with ligands of interest in solution and then contacted with an excess of streptavidin-conjugated 10 nm gold particles. Samples can be treated with 2% phosphotungstic acid (pH 7.0, 30 sec) to enhance contrast. Images of random fields were acquired for each treatment and analyzed for formation of ConA complexes. Gold particles within 25 nm of less of each other were considered to be part of a complex. This distance was based on the modeled [lenght] length of the synthetic [multivalnet] multivalent ligands used [23] and the structure of tetrameric ConA determined by X-ray crystallographic analysis[97].

Page 50, first full paragraph

Jurkat cells were cultured and maintained as previously described [94]. Cells were washed three times in cold PBS and then treated with Hoescht 33342 (100 μg/mL) for 30 minutes at 30 °C. Cells were washed twice with cold PBS and then fixed for 30 minutes at 4 °C with 2% paraformaldehyde in HEPES pH 7.4. Fixed cells were washed twice and then treated in 200 μL final volume with premixed solutions of Con A and scaffold. A 2x solution of Con A and scaffold was prepared in PBS pH 7.2, vortexed briefly, and then incubated at 22 °C for 30 minutes before being added to cells. Cells, Con A solutions, and 100 μg/mL DNAse (to prevent cell aggregation by nucleic acid) were incubated at 22 °C for 30 minutes. Cells were pelleted at 400 xg, resuspended gently into 50 μL PBS, and then added to slides for visualization at 200 x magnification on a Zeiss Axioscope outfitted with the appropriate filter set. Approximately 100 - 200 cells were counted from random fields on each day. Clusters were scored for at least two cells in direct contact with each other and expressed as a percentage of the total number of objects (individual cells and clusters) counted. Results are [summariezed] summarized in Fig. 10. ROMP-derived ligands **9-12** alone were not able to cause cell aggregation. Images were captured in IPlab Spectra 3.2 and prepared in Adobe Photoshop 5.0.

Page 52, second full paragraph

Those of ordinary skill in the art will appreciate in view of the descriptions herein that there are a variety of alternative structures, methods, procedure and techniques that can be readily applied or adapted to the practice of this invention other than those that have been specifically exemplified. It will be appreciated that there are a wide variety of designs for and methods for preparation of multivalent ligands with properties as described herein. It will also be appreciated that there are a wide variety of molecular [scaffold] scaffolds available for the productive presentation of SRE as well as a wide variety of SRE that can be applied or adapted to the methods described herein.

MARKED-UP AMENDMENTS TO CLAIMS

USSN 09/ 815,296

10. The method of claim 6 [wherien] wherein the multivalent ligand inhibits chemotaxis of the prokaryotic cell.

17. The method of claim [1] 2 wherein the cell is a eukaryotic cell.

21. The method of claim 17 wherein the eukaryotic cell is a cell of the immune [systems] system.

25. The method of claim 24 wherein one or more of the signal recognition [element] elements is a formylated peptide and wherein the multivalent ligand comprises a plurality of formylated peptides covalently bonded to a molecular scaffold.

31. The method of claim 30 wherein the multivalent ligand comprises a signal recognition element that is an epitope foreign to the [orgnaism] organism from which the B-cell or T-cell originates.

38. The method of claim 30 wherein [wherein] the multivalent ligand comprises at least one signal recognition element that is a self epitope which is recognized as a foreign epitope by the B-cell or T-cell.

45. The method of claim 44 wherein the multivalent ligand modifies the immune response to the foreign [anitgen] antigen or epitope and wherein the multivalent ligand comprises a signal recognition element that is an epitope or antigen that is recognized as foreign by the immune cell, cells or immune system that mediates the immune response.

47. The method of claim 46 wherein the multivalent ligand modifies the immune response to an antigen or epitope that is recognized as self and wherein the multivalent ligand comprises a signal recognition element that is an epitope or antigen that is recognized as self by the immune cell[.],cells or immune system.

52. A pharmaceutical composition for treating a bacterial infection which comprises an amount of a multivalent ligand effective for inhibiting the chemotaxis response in the bacterium, wherein the multivalent ligand comprises a plurality of signal recognition elements that are chemoattractant signals covalently bonded to a molecular scaffold, and a pharmaceutically acceptable carrier.

60. The method of claim 59 wherein one or more of the recognition elements [bind] binds to a protein.

61. The method of claim 59 wherein one or more of the functional elements [are] is a label or a reporter group.

62. The method of claim 1 wherein one or more of the signal recognition [element] elements is selected from the group consisting of an amino acid, a peptide, a protein, a derivatized peptide, a monosaccharide, a disaccharide, a polysaccharide, a nucleic acid, a cell nutrient, an [eptiope,] epitope, an antigenic determinant, a hapten, or a cell surface [recpetor.] receptor.

63. The method of claim 1 wherein one or more of the signal recognition [element] elements is a saccharide or a derivatized saccharide.

64. The method of claim 1 wherein one or more of the signal recognition [element] elements is a peptide or a derivatized [pepetide.] peptide.

65. The method of claim 1 wherein one or more of the signal recognition [element] elements is a protein.

66. The method of claim 1 wherein one or more of the signal recognition [element] elements is an N-formyl peptide.

67. The method of claim 1 wherein one or more of the signal recognition [element] elements is an epitope.

69. The method of claim 1 wherein the multivalent ligand comprises [between] 2 to about 10 signal recognition elements.

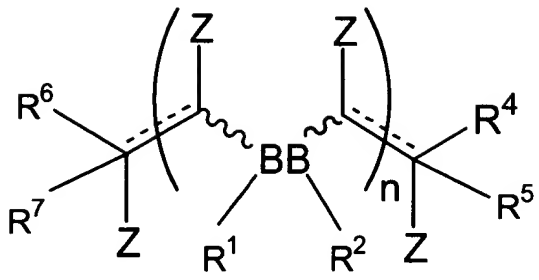
70. The method of claim 1 wherein the multivalent ligand comprises [between] about 10 to 25 signal recognition elements.

76. The method of claim 75 wherein the multivalent ligand further [comrpises] comprises a plurality of recognition elements [covalenly] covalently bonded to the scaffold wherein the signal recognition elements are in turn noncovalently bonded to one or more recognition elements.

79. The method of claim 78 wherein the [lectin is] lectins are [Concanavalin] Concanavalin A.

80. The method of claim 1 wherein the molecular scaffold is selected from the group consisting of a polyacrylamide, a polyester, a polyether, a polymethacrylate, a polyol, and a polyamino [acids] acid.

82. The method of claim 1 wherein the multivalent ligand has the structure:



wherein:

n is an integer that is 2 or more which represents the number of repeating units within the [paraentheses] parentheses in the ligand;

the dashed lines indicate optional double bonds;

"BB" represents the backbone repeating unit, which may be cyclic or acyclic, and may be the same or different in a random or block arrangement, the wavy lines indicating that a BB unit may be in either a cis or trans configuration in the ligand backbone;

each R^1 and R^2, independently of other R^1 and R^2 in the ligand, can be H or an organic group, a recognition element -L^2-RE, a functional element -L^3-FE or a signal recognition element -L^1-SRE or both of R^1 and R^2 can be the -L^1-SRE group;

wherein L^{1-3}, independently, represent [an] optional linker groups which may be the same or different in different repeating units;

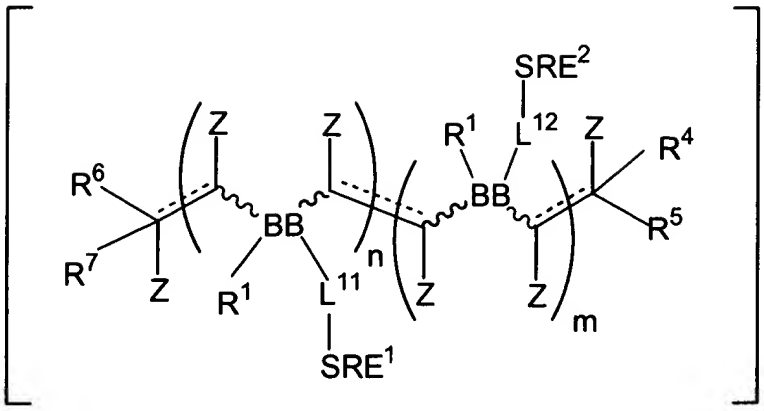
R^4 and R^5 are H, or an organic group;

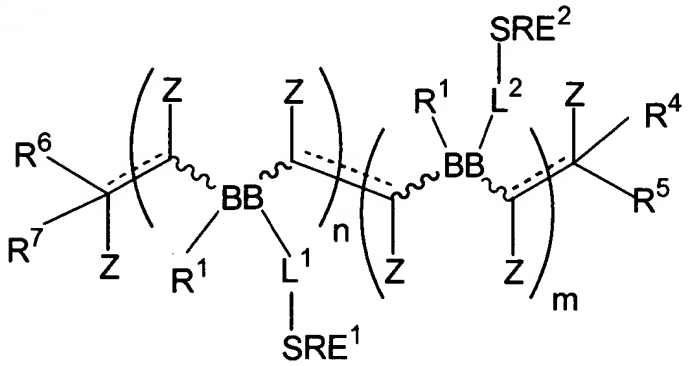
R^6 and R^7 are H, an organic group or an end-group; and

Z , independently of other Z in the ligand, is H, OH, OR^8, SH, a halide (F, Br, Cl, I), NH_2 or $N(R^8)_2$, where R^8 is H or an organic group or Z is absent when the optional double bond is present.

83. The method of claim 82 wherein SRE is a peptide or a derivatized peptide.

91. The method of claim 82 wherein the multivalent ligand has the structure:





wherein:

m + n is 2 or more;

dashed lines indicate the presence of optional double bonds;

"BB" represents the backbone repeating unit, which may be cyclic or acyclic, and may be the same or different in a random or block arrangement and wavy lines indicate that the BB unit may be in a cis or trans configuration in the backbone of the repeating unit;

each R^1, independent of other R^1 in the ligand, can be H or an organic group;

[L^{11} and L^{12}] L^1 and L^2, which may be the same or different, represent [an] optional linker [group] groups;

SRE^1 and SRE^2 represent two different signal groups;

R^4 and R^5 are H, an organic group or an end-group;

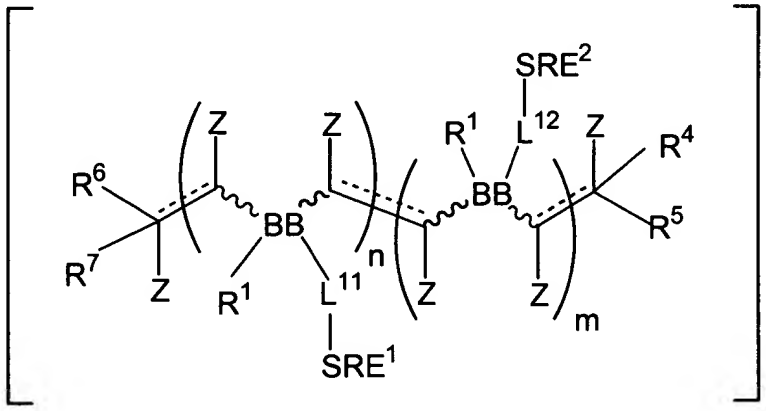
R^6 and R^7 are H, an organic group or an end-group; and

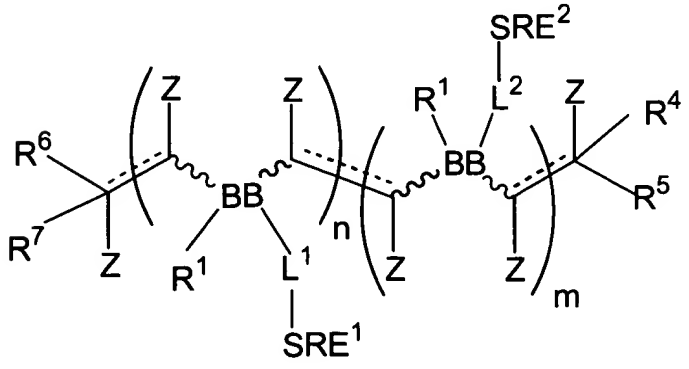
Z , independently of other Z in the polymer, is H, OH, OR^8, SH, a halide (F, Br, Cl, I), NH_2 or $N(R^8)_2$ where R^8 is H or an organic group or Z is absent when a double bond is present.

95. The method of claim 91 wherein one of SRE^1 or SRE^2 is an [epitopes] epitope and the other of SRE^1 or SRE^2 binds to a cell surface receptor of an immune cell.

100. The [mulivalent] multivalent ligand of claim 99 wherein the FE in the at least one $-L^2-FE$ group in the ligand is a detectible label or a reported group.

107. The multivalent ligand of claim 96 having the structure:





wherein:

m + n is an integer of 2 or more and each integer represents the number of [repeting] repeating units in the parentheses;

each Y, independent of other Y in the ligand, is -O-, -S-, -NR^8-, or -CH_2-;

R^1 can be H, an organic group, a -L^2-RE group or an -L^3-FE group;

[L^{11} and L^{12}] L^1 and L^2, which may be the same or different, represent optional linker groups;

SRE^1 and SRE^2 represent two different signal recognition elements;

R^4 and R^5 are H, an organic group or an end-group; and

R^6 and R^7 are H, an organic group or an end-group.

110. The multivalent ligand of claim 107 wherein one of SRE^1 or SRE^2 is an epitope and [the] the other of SRE^1 or SRE^2 binds to an immune cell.

124. The method of claim 122 wherein the biological particles are [cell] cells, viruses or virions.

126. A method for inducing or enhancing induction of apoptosis in a cell which comprises the steps of:

forming a multivalent ligand which comprises a plurality of signal recognition elements which bind to the cell and induce apoptosis in the cell and contacting the [cells] cell with the multivalent ligand.

127. The method of claim 126 wherein one or more of the signal recognition [element] elements is a lectin.